Am. J. Trop. Med. Hyg., 98(5), 2018, pp. 1512–1519
doi:10.4269/ajtmh.17-0564

Frequent Community Use of Antibiotics among a Low-Economic Status Population in Manila, the Philippines: A Prospective Assessment Using a Urine Antibiotic Bioassay

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Abstract. The widespread unregulated use of antibiotics without medical consultation contributes to the burden of antibiotic resistance in Southeast Asian countries. This study investigated antibiotic use before hospital consultation. In a prospective observational study from February 2, 2015, to July 2, 2015, we enrolled febrile patients attending the emergency room in San Lazaro Hospital, Manila, the Philippines. A urine sample was collected and a bioassay was used to detect antibiotic activity in urine using *Bacillus stearothermophilus* (ATCC7953), *Escherichia coli* (ATCC25922), and *Streptococcus pyogenes* (ATCC19615). Patients or caregivers reported their medication history, clinical information, and socioeconomic status. During the study period, 410 patients were enrolled. The median (interquartile range) age was 14 (7–23) years and 158 (39%) reported prior antibiotic use, predominantly a beta-lactam antibiotic. A total of 164 (40%, 95% confidence interval [CI]: 35–45) patients were urine bioassay positive with any of three organisms. The *Bacillus* assay was the most sensitive, detecting 162 (99%, 95% CI: 96–100) cases. Among bioassay positive patients, dengue ($N = 91$, 55%, 95% CI: 48–63) was the most frequent diagnosis, followed by other viral infections, including measles, rubella, and mumps ($N = 17$, 10%, 95% CI: 6–16). Patients with a positive bioassay were significantly more likely to be from the lowest-income group (adjusted odds ratio [AOR]: 1.7; 95% CI: 1.1–2.6) and required hospital admission (AOR: 2.1; 95% CI: 1.3–3.5). Unnecessary antibiotic use for febrile illnesses before hospital consultation is common in a low-income, highly populated urban community in Manila. Education targeting this group should be implemented to reduce unnecessary antibiotic use.

INTRODUCTION

Antibiotic resistance is a major public health problem worldwide.[1] The rapid emergence and spread of antibiotic resistance have been reported in many countries.[2,3] Infections with antibiotic resistant organisms are associated with higher mortality, prolonged illness, and increased health-care costs because of additional diagnostic tests and antibiotic therapies.[4,5] Unregulated use of antibiotics is common in many resource-limited countries and one of the factors contributing to the high prevalence of antibiotic resistance.[1,6,7]

In the Philippines, despite the existing legislative framework to control antibiotic use, the unregulated sale of antibiotics without medical prescription is widespread.[8,9] Even those with a low-income can afford to purchase low-priced generic antibiotics without a medical consultation. People may prefer antibiotics over the counter because of the possible additional costs, efforts, and time incurred when visiting health facilities.[9] The widespread use of antibiotics before medical consultation can result in a significantly lower yield of the causative pathogen in microbiology tests.[10,11] This can lead to misdiagnosis, delay of proper treatment, and poor surveillance of resistance.

Understanding the prevalence of community antibiotic use is useful information for providing a more appropriate medical management in health care facilities and for developing stewardship strategies to control resistance in the community. Several studies have shown that self-reporting by patients or caregivers about the history of recent antibiotics can be unreliable.[12] Laboratory bioassay methods have been used to detect antibiotic activity in body fluid specimens as a measure of antibiotic use.[13,14] Relatively high rates of antibiotic use detected by the bioassay have been reported in Southeast Asia.[15–17] Limited information is available on the prevalence of antibiotic use before medical consultation in low-income communities in the Philippines. We conducted a prospective hospital-based observational study investigating prior antibiotic use in patients attending the San Lazaro Hospital (SLH) for a medical consultation.

MATERIALS AND METHODS

Setting. We performed a prospective observational study, in single health facility in Manila City, Metro Manila (officially called as National Capital Region), the Philippines. The SLH is a 500-bed tertiary hospital specializing in infectious diseases. This national government hospital is the National Infectious Disease Referral Center and is also a major care provider for people from the low-income area in Manila city. This hospital is located in one of the most economically depressed and densely populated districts in the country. Although SLH is a tertiary care referral hospital, most outpatients in the emergency room (ER) are walk in and live around the hospital.

Patients. This study was conducted each weekday between 9 AM and 4 PM from February 2, 2015 to July 2, 2015. All patients aged more than 12 months who presented with fever or a history of fever with onset within the last 2 weeks were enrolled during the recruitment period. Subjects aged less than 12 months , previously diagnosed with human immunodeficiency virus (HIV), with on-going treatment of tuberculosis (TB), or a history of hospital admission within the previous month were excluded. Subjects unable to provide urine were also excluded from this study.

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Samples and data. After providing written informed consent, sociodemographic and clinical information of the patient or patient's caregiver were collected using a standard questionnaire. Socioeconomic information included area of residence and patient's or caregiver's monthly income. The clinical diagnosis made by the attending physician, the physical examination findings, antibiotic use during this illness, and the name of antibiotics were documented by the researcher. Urine samples were collected before the initiation of antibiotics in the hospital. The samples were promptly transported to the laboratory for aliquoting and storage in a –80°C freezer until later testing in the bioassay. Twenty urine samples of healthy volunteers with no history of consumption of any antibiotics within the previous 2 weeks were also obtained as negative controls.

Laboratory methods. A disc diffusion method, as previously described by Liu et al.,[18] was used to measure antibiotic activity in the urine samples. Three indicator organisms prepared to a 0.5 Macfarland concentration were inoculated on agar in Petri dishes. Mueller-Hinton agar was used for the *Bacillus stearothermophilus* (ATCC 7953) and *Escherichia coli* (ATCC 25922), Mueller-Hinton agar with 5% sheep blood was used for *Streptococcus pyogenes* (ATCC 19615). Three microliters of urine was applied to 6-mm diameter discs of sterile filter paper which had been placed on the lawns of each organism. The plates of *S. pyogenes* and *E. coli* were incubated at 35°C and at 56°C for *B. stearothermophilus* for 18–24 hours. After incubation, the zone diameter of inhibited bacterial growth surrounding each filter paper disc was measured.

Data analysis. Statistical analysis of patient characteristics and urine bioassay result was conducted using the χ^2 test or Fisher's exact test for categorical variables and the *t* test for numerical variables. To investigate the effect of various variables on prior antibiotic use and hospitalization as required by the attending physician, an unadjusted and adjusted logistic regression model was used. Adjusted models included values for age group (1–4, 5–18, 19–64, 64 over years old), sex, duration of symptom, living area, and symptoms which were significant relation with the urine bioassay result. Data were managed using Microsoft Access, and statistical analyses were performed using the Stata software (Stata Statistical Software Release 13; Stata Corp., College Station, Texas). Values of $P < 0.05$ were considered significant.

Ethical consideration. All participants, or for children their parent or guardian, were asked to give informed written consent at the time of enrollment. Ethical approval was obtained from the Research and Ethical Review Board of SLH, the Philippines, and the Institutional Review Board of the Institute of Tropical Medicine, Nagasaki University, Japan.

RESULTS

The total number of patient consultations in the ER was 8,375 during the study period. One thousand three hundred and twenty three patients visited from Monday to Friday between 9 AM and 4 PM. Among them, 545 subjects were excluded because the reason for consultation was after an animal bite ($N = 53$), they were being treated for TB or HIV ($N = 21$), aged less than 1 year ($N = 85$), not a febrile illness ($N = 361$), refused ($N = 9$) and were unable to provide urine ($N = 16$). Among possibly eligible subjects, 410 (53%) patients agreed to be enrolled in this study. For organizational reasons, the remaining 368 patients were not seen by the study team. The examination of the ER ledger for these patients revealed that some may have been eligible for the study but it was not possible to determine the exact number.

The urine bioassay was positive for antibiotic activity for any of the three organisms in 164 (40%, 95% confidence interval [CI]: 35–45) samples. One hundred and sixty two (99%, 95% CI: 96–100) of the positive samples were detected by the plates with *B. stearothermophilus*. The plates with *E. coli* and *S. pyogenes* detected 85 (52%, 95% CI: 44–60) and 120 (73%, 95% CI: 66–80) of any positive assay, respectively. Although the assay of *S. pyogenes* was not able to detect further cases additional with *B. stearothermophilus*, the assay of *E. coli* showed further two cases (1.2%, 95% CI: 0.1–4). According to the self-reports, in these two additional cases co-trimoxazole and ciprofloxacin had been taken. None of the 20 healthy volunteers had antibiotic activity detected in their urine.

Table 1 shows the relationship between patient antibiotic use based on self-reports and the bioassay. The urine bioassay showed 122 (80.8%, 95% CI: 73.6–86.7) positive urine assays among subjects who reported to take antibiotics during the illness. There were 42 (16.2%, 95% CI: 11.9–21.3) positive urine assays among subjects who reported not taking antibiotics and 29 (19.2%, 95% CI: 13.2–26.4) subjects who reported antibiotic use but showed a negative urine assay. The positive predicted value and negative predict value of self-reports were 80.8% and 83.8%, respectively.

According to patients' self-reporting, the main source of antibiotics was community pharmacies followed by private clinics and public health centers (Tables 2). None of the patients reported obtaining medication from friends, relatives, or charities. Most antibiotics were beta-lactams including amoxicillin, cloxacillin, amoxicillin/clavulanate, and oral cephalosporins. The usage of fluoroquinolones was small (8%). Most of the patients took antibiotics for less than 7 days (91%).

Dengue fever was most the common clinical diagnosis among enrolled patients ($N = 200$, 48.8%, 95% CI: 43.8–53.7) and patients with positive urine bioassay ($N = 91$, 55.5%, 95% CI: 47.5–63.2) (Table 3). This was followed by other viral infection, such as measles, rubella, mumps ($N = 17$, 10.4%, 95% CI: 6.2–16.1), upper respiratory infection ($N = 14$, 8.5%, 95% CI: 4.7–13.9), and acute gastroenteritis ($N = 14$, 8.5%, 95% CI: 4.7–13.9).

The association between the characteristics of enrolled patients and the urine bioassay results is shown in Table 4. There was no significant difference in the age group, sex, and the living area between the subjects with the positive and negative result. Patients presenting with a rash were less likely to have a positive urine bioassay but patients presenting with abdominal pain or arthralgia were more likely to have a positive result. A longer duration of symptoms was observed in

TABLE 1

Relationship between patients self-reported antibiotic use and urine bioassay results

	Positive urine bioassay	Negative urine bioassay
	$N = 144$	$N = 246$
Self-reported antibiotic use	*n* (%)	*n* (%)
Yes $N = 151$	122 (80.8)	29 (19.2)
No $N = 259$	42 (16.2)	217 (83.8)

TABLE 2
Characteristics of the self-reported antibiotic use and the proportion with antibiotics detected and not detected by urine bioassay

	Self-reported *n* (%)	Urine antibiotic activity detected *n* (%)	Urine antibiotic activity not detected *n* (%)	*P* value*
Total	151 (36.8)	122 (80.8)	29 (19.2)	–
Source of antibiotic				
Pharmacy	91 (60.3)	70 (57.4)	21 (72.4)	0.454
Private clinic	25 (16.6)	21 (17.2)	4 (13.8)	
Public health center	22 (14.6)	20 (16.4)	2 (6.9)	
Hospital	13 (8.6)	11 (9.0)	2 (6.9)	
Antibiotic taken				
Amoxicillin	35 (23.2)	28 (23.0)	7 (24.1)	0.081
Cloxacillin	25 (16.6)	22 (18.0)	3 (10.3)	
Amoxicillin/ clavulanate	24 (15.9)	20 (16.4)	4 (13.8)	
Oral cephalosporins	12 (8.0)	12 (9.8)	0 (0)	
Co-trimoxazole	18 (11.9)	14 (11.5)	4 (13.8)	
Fluoroquinolones	8 (5.3)	5 (4.1)	3 (10.3)	
Macrolide	3 (2.0)	2 (1.6)	1 (3.5)	
Chloramphenicol	2 (1.3)	0 (0.0)	2 (6.9)	
Metronidazole	2 (1.3)	1 (0.8)	1 (3.5)	
Others	4 (2.7)	4 (3.3)	0 (0)	
Unknown	18 (11.9)	14 (11.5)	4 (13.8)	
Duration of antibiotics				
1 day	49 (32.5)	38 (31.2)	11 (37.9)	0.016
2–3 days	64 (42.4)	55 (45.1)	9 (31.0)	
4–6 days	23 (15.2)	21 (17.2)	2 (6.9)	
More than 1 week	15 (9.9)	8 (6.6)	7 (24.1)	
Living area				
Manila city	64 (42.4)	51 (41.8)	13 (44.8)	0.943
Metro Manila but outside Manila city	72 (47.7)	59 (48.4)	13 (44.8)	
Outside Metro Manila	15 (9.9)	12 (9.8)	3 (10.3)	
Monthly income (PHP)†				
≥ 5,000	56 (37.1)	43 (32.3)	13 (44.8)	< 0.05
< 5,000	95 (62.9)	79 (64.8)	16 (55.2)	

* Pearson's χ^2 test, comparing mean between urine bioassay positive and negative.
† PHP = Philippines peso (100 PHP = 2 US dollar).

patients with a positive urine bioassay. Significant differences in the proportion with a positive bioassay were observed between the low income group (income < 5,000 Philippine pesos [PHP]/month) and the higher income group (income ≥ 5,000 PHP/month) (adjusted odds ratio [AOR]: 1.78; 95% CI: 1.17–2.72). Furthermore, a higher risk of subsequent admission from the ER was observed among patients who had taken antibiotics before their consultation as indicated by a positive urine bioassay (unadjusted odds ratio [OR]: 2.50; 95% CI: 1.56–4.00, AOR: 1.96; 95% CI: 1.17–3.29; Table 5).

TABLE 3
Clinical diagnosis at emergency room in the San Lazaro Hospital and the results of urine antibiotic bioassay

	Total	Urine antibiotic activity detected
	N = 410	*N* = 164
	n (%)	*n* (%)
Dengue	200 (48.8)	91 (55.5)
Upper respiratory infection	31 (7.6)	14 (8.5)
Lower respiratory infection	27 (6.6)	7 (4.2)
Acute gastroenteritis	27 (6.6)	14 (8.5)
Urinary tract infection	15 (3.7)	3 (1.8)
Other viral infection (including measles, rubella, mumps)	79 (19.3)	17 (10.4)
Enteric fever	7 (1.7)	4 (2.4)
Soft tissue infection	2 (0.5)	2 (1.2)
Others	19 (4.6)	11 (6.7)
Unknown	3 (0.7)	1 (0.6)

DISCUSSION

This study, using an objective urinary bioassay, has demonstrated that a high proportion of people used antibiotics before hospital consultation in a low-income urban population in the Philippines. According to the diagnosis by the attending physician in the hospital, dengue was by far the most common diagnosis and most antibiotics were unnecessary.

Our study found that a substantial proportion of patients/caregivers reported taking the antibiotics which were purchased in a local pharmacy. We were unable to identify whether the purchases were based on the doctor's prescription. We assume that certain proportion of our enrolled subjects purchased antibiotics without medical consultation or prescription. In the Philippines, although a medical prescription is officially required to obtain antibiotics, recent reports indicate that inappropriate selling of antibiotics without prescription occurs in community drug stores.[9]

We found a significant association between the monthly income of patients and a positive urine bioassay result. The average income per month in the Philippines is about 9,449 Philippine Peso which is equivalent to 215 US dollars.[19] The economic status of our studied population was lower than this average. In Manila, inexpensive generic antibiotics are widely available.[8,9] We recently visited three local community pharmacies where antibiotics were available without a prescription and generic antibiotics were available at low cost: amoxicillin/capsule (500 mg) 5.5–6.6 PHP (0.11–0.13 US dollar);

TABLE 4
Associations between patient characteristics and the urine bioassay result

	Urine bioassay result			
	Negative *n* (%)	Positive *n* (%)	Unadjusted OR (95% CI)	AOR* (95% CI)
Overall	246 (60.0)	164 (40.0)	–	–
Sex (male)	139 (56.5)	104 (63.1)	1.33 (0.89–2.00)	1.35 (0.88–2.08)
Age group (years old)				
1–4	93 (37.8)	59 (36.0)	Ref	Ref
5–18	42 (17.1)	19 (11.6)	0.71 (0.38–1.34)	0.90 (0.45–1.81)
19–64	110 (44.7)	82 (50.0)	1.18 (0.76–1.81)	1.30 (0.81–2.08)
64 over	1 (0.4)	4 (2.4)	6.31 (0.69–57.8)	8.12 (0.82–80.81)
Symptom				
Cough	117 (47.6)	88 (53.7)	1.28 (0.86–1.90)	–
Headache	161 (65.5)	110 (67.1)	1.08 (0.71–1.63)	–
Sputum	82 (33.3)	67 (40.9)	1.38 (0.92–2.08)	–
Runny nose	74 (30.1)	59 (36.0)	1.31 (0.86–1.99)	–
Sore throat	77 (31.3)	52 (31.7)	1.02 (0.67–1.56)	–
Dyspnea	70 (28.5)	52 (31.7)	1.17 (0.76–1.79)	–
Abdominal pain†	110 (44.7)	91 (55.5)	1.54 (1.04–2.29)	1.40 (0.91–2.15)
Diarrhea	27 (11.0)	24 (14.6)	1.39 (0.77–2.51)	–
Rash†	103 (41.9)	48 (29.3)	0.57 (0.38–0.88)	0.59 (0.38–0.93)
Myalgia	92 (37.4)	62 (37.8)	1.02 (0.68–1.53)	–
Arthralgia†	87 (35.4)	75 (45.7)	1.54 (1.03–2.31)	1.59 (1.01–2.51)
Mean duration of symptom (days)‡	4.3	5.1	1.11 (1.03–1.19)	1.11 (1.03–1.20)
Living area				
Manila city	116 (47.2)	72 (43.9)	Ref	Ref
Metro Manila but outside Manila city	104 (42.3)	78 (47.6)	1.21 (0.80–1.83)	1.13 (0.72–1.77)
Outside Metro Manila	26 (10.6)	14 (8.5)	0.87 (0.47–1.77)	0.59 (0.27–1.31)
Monthly income (PHP)†				
≥ 5,000	123 (50.0)	57 (34.8)	Ref	Ref
< 5,000	123 (50.0)	107 (65.2)	1.88 (1.25–2.82)	1.75 (1.15–2.68)

AOR = adjusted odds ratio; CI = confidence interval; OR = odds ratio; PHP = Philippines peso (100 PHP = 2 US dollar); Ref = reference.
* Adjusted for age group, sex, duration of symptom, living area, presence of rash, presence of abdominal pain, presence of arthralgia, and monthly income group.
† $P < 0.05$ by Pearson's χ^2 test, comparing proportion between urine bioassay positive and negative group.
‡ $P < 0.05$ by t test, comparing mean between urine bioassay positive and negative group.

amoxicillin/clavulanate/tablet (500/125 mg) 25–50 PHP (0.5–1 US dollar); trimethoprim-sulfamethoxazole/tablet (800/160 mg) 5–10 PHP (0.1–0.2 US dollar); and levofloxacin/tablet (500 mg) 25–45 PHP (0.5–0.9 US dollar). Although most public health clinics provide free medical consultation and drugs, we speculate that patients/caregivers obtain antibiotics in their local pharmacies because they might consider the cost higher in medical facilities than the cost in the pharmacy due to their poor knowledge. Long waiting time in health facilities is considered to be another factor leading people to go to the pharmacy without medical consultation in Manila.

A few other studies have described a relationship between economic status and antibiotic use.[20,21] The opposite result from our finding was observed in Nigeria in that children with a higher socioeconomic status were more likely to have consumed antibiotics before the consultation to tertiary hospitals.[22] The authors of this study suggested that children living in a higher-economic status area tended to go to private clinics which were more likely to prescribe antibiotics. In our setting, most patients attending this hospital had a low-income and, in contrast with the study in Nigeria, there were very few with a high-income. There may also be a relationship between low economic status and low educational attainment although our study did not determine the educational level of subjects. A study in Albania found that people with low education level were more likely to use antibiotics without prescription.[23] These results suggested that to reduce unnecessary antibiotic use, it is important to provide knowledge and education about acute febrile illness targeting the low-income group.

Studies about antibiotic use before the medical consultation using a laboratory bioassay to detect antibiotic activity in a body fluid have been conducted in various settings (Table 6). The inclusion criteria in these studies and their target population have varied (e.g., children or adults, outpatients or inpatients, and febrile or all patients).[11,12,15–18,22,24–33] In view of the different inclusion criteria it is difficult to compare the antibiotic use in different settings. Furthermore, the various types of body fluid specimen and indicator organisms were used in each study. The results of antibiotic use reported by previous studies have varied between 20% and 80% (Table 6). Recent studies in Cambodia and Laos using a urine bioassay method similar to ours showed that 32% and 50% of outpatients had urinary antibiotic activity, respectively.[15,16] Our prevalence of urine antibiotic activity (40%, 95% CI: 34–47) was similar to these results from Southeast Asian countries. We observed a higher level of agreement between self-reported antibiotic use and antibiotic activity detected in the urine than those of other previous reports (Table 6). Among patients/caregivers who reported taking antibiotics before their medical consultation, our urine assay detected antibiotic activities in 80.8% (95% CI: 67–96). Most patients enrolled in our study were able to name the antibiotic they had used. A previous study study conducted in the Philippines in 1980s showed a significant gap between the self-reports and evidence of antibiotic activity.[28] The results of our current study suggest that the self-reporting of antibiotic use was relatively reliable in this area and that people have awareness of their antibiotic use at a community level.

Significant relationships between antibiotic use and some symptoms were found. While patients who had abdominal

TABLE 5
Associations between patient characteristics on admission, the urine bioassay result and the patients that required hospitalization

	Required hospitalization to SLH			
	No	Yes	Unadjusted	
	n (%)	*n* (%)	OR (95% CI)	AOR* (95% CI)
Total	122 (29.8)	287 (70.2)	–	–
Sex (male)	71 (58.2)	172 (59.9)	1.07 (0.70–1.65)	1.04 (0.64–1.70)
Age group				
1–4	38 (31.2)	113 (39.4)	Ref	Ref
5–18	19 (15.6)	42 (14.6)	0.74 (0.69–1.43)	1.21 (0.54–2.71)
19–64	64 (52.5)	128 (44.6)	0.67 (0.42–1.08)	0.76 (0.43–1.33)
65 over	1 (0.8)	4 (1.4)	1.35 (0.15–12.40)	0.90 (0.80–10.15)
Presence of symptoms during the febrile illness				
Cough	61 (50.0)	144 (50.2)	1.01 (0.66–1.54)	–
Headache	77 (63.1)	193 (67.3)	1.20 (0.77–1.87)	–
Sputum	47 (38.5)	102 (35.5)	0.88 (0.57–1.36)	–
Runny nose	44 (36.1)	89 (31.0)	0.80 (0.51–1.24)	–
Sore throat	41 (33.6)	88 (30.7)	0.87 (0.56–1.37)	–
Dyspnea	30 (24.6)	92 (32.1)	1.45 (0.89–2.34)	–
Abdominal pain†	40 (32.8)	160 (55.8)	2.58 (1.65–4.03)	2.11 (1.28–3.47)
Diarrhea†	5 (4.1)	46 (16.0)	4.46 (1.73–11.53)	5.85 (1.94–17.60)
Rash	47 (38.5)	104 (36.2)	0.91 (0.59–1.40)	–
Myalgia†	31 (25.4)	122 (42.5)	2.17 (1.36–3.47)	1.52 (0.84–2.76)
Arthralgia†	31 (25.4)	130 (45.3)	2.43 (1.52–3.89)	2.01 (1.14–3.56)
Duration of symptom (mean days)‡	3.7	5	1.26 (1.12–1.41)	1.23 (1.09–1.38)
Comorbidity§	28 (23.1)	54 (18.8)	1.26 (1.12–1.41)	0.84 (0.47–1.50)
Living area†				
Manila city	73 (59.8)	114 (39.7)	Ref	Ref
Metro Manila but outside Manila city	40 (32.8)	142 (49.5)	2.27 (1.44–3.59)	2.29 (1.43–3.66)
Outside Metro Manila	9 (7.4)	31 (10.8)	2.21 (0.99–4.90)	1.63 (0.70–3.76)
Monthly income (PHP)				
≥ 5,000	61 (50.0)	119 (41.5)	Ref	–
< 5,000	61 (50.0)	168 (58.5)	1.41 (0.92–2.16)	–
Prehospital antibiotic use confirmed by urine bioassay†	31 (25.4)	132 (50.0)	2.50 (1.56–4.00)	1.99 (1.17–3.39)

AOR = adjusted odds ratio; CI = confidence interval; OR = odds ratio; PHP = Philippines peso (100 PHP = 2 US dollar); Ref = reference; SLH = San Lazaro hospital.
* Adjusted for age group, sex, duration of symptom, living area, presence of any comorbidity, presence of abdominal pain, presence of diarrhea, presence of myalgia, presence of arthralgia, rash.
† $P < 0.05$ by Pearson's χ^2 test, comparing proportion between patients required to be admitted to SLH and those who was not required.
‡ $P < 0.05$ by t test, comparing mean between patients required to be admitted to SLH and those who were not required.
§ Subjects who have a comorbidity were defined as patients who had taken regular medicine for chronic diseases.

pain or arthralgia were more likely to take antibiotics before medical consultation, patients presenting with a rash were less likely to take antibiotics. This may be because patients/caregiver tend to consider that a rash indicates a serious condition that should be seen at a hospital whereas abdominal pain or arthralgia may be considered less serious and for which antibiotics may be taken without medical consultation. Abdominal pain is a common symptom in dengue patients and one of the important warning signs.[34] Because dengue fever is a very common infectious disease in Philippines and antibiotic use is not necessary, these factors suggested that the education for people who had abdominal pain is also necessary in dengue endemic area.

Several different bacteria have been used as indicator organisms in the urinary bioassay. Almost 99% of positive samples in this study were detected using *B. stearothermophilus*. Similar findings were obtained in studies in Cambodia and Laos.[15,16] It is possible the assay process could be simplified by using only one organism. This will depend on the local pattern of antibiotic use; fluoroquinolones, not commonly used in these three settings but common in others, may not be reliably detected using *B. stearothermophilus*.[15,16]

There are several limitations in our study. We calculated that only 53% of potentially eligible patients agreed to participate in the study. This was based on the examination of the ER ledger for patients we missed being able to approach. We could not be sure that the missed patients would have been eligible, but this did introduce a probable selection bias. The study period was only during the daytime and in the dry season. During the rainy season in the Philippines, the number of consultation increases due to dengue fever, leptospirosis, and acute gastritis. Thus, the study may not be fully representative of febrile patients seen at the ER in the SLH. Our study subjects were mainly drawn from a low-economic status population, did not include middle and high income participants, and therefore may not be a representative of community antibiotic use in a fully representative population in the Philippines. The urine bioassay could underestimate antibiotic use as it may only detect some antibiotics, such as beta-lactams and erythromycin, for 12–24 hours after taking a single dose.[32] We did not determine the timing of antibiotic exposure in relation to the time of the urine sample which might have added more precision to our estimates. Moreover, antibiotics, such as chloramphenicol and doxycycline, are predominantly metabolized by the liver with only a small proportion of antibiotic excreted in the urine.[13] According to self-reports of antibiotic use in our enrolled subjects, the use of these antibiotic was uncommon. Freezing and thawing of the urine sample may have led to a loss of antibiotic activity. False positive results may occur due to other agents present in the urine exerting antibacterial activity.[16] Recall bias by the patient/caregiver may lead to an inaccurate measure of self-reported antibiotic consumption. We were also unable to confirm the diagnosis of enrolled

TABLE 6

Previous studies analyzing antibiotic use before medical consultation using a bioassay to measure antibiotic use

Study site	Bioassay sample	Year	Target population	Criteria	Number tested	Reporting antibiotic use (%)	Positive bioassay (%)	Bacteria used in the laboratory assay
Philippines[28]	Serum	1984–1986	Children < 5 years	ALRI	530	51.6	27.9	*Staphylococcus aureus*
	Urine	1984–1986	Children < 5 years	ALRI	346	NR	32.3	*S. aureus*
Uruguay[27]	Urine	1987–1988	Children < 5 years	ALRI	90	NR	64.4	*Bacillus megaterium*
Philippines[12]	Urine	1989–1990	Children < 5 years	ALRI	108	55	84	*S. aureus*
Argentina[25]	Urine	NR*	Children < 5 years	ALRI	424	40	72	*Bacillus subtilis*
Kenya[24]	Urine	1994–1996	Adults	ALRI	248	NR	54	*S. aureus*
Kenya[31]	Plasma	1998–2002	Children (≤ 13 y/o)	All admitted patients	16,570	NR	3.5–11‡	*S. aureus*
Taiwan[18]	Urine	NR†	Mainly adults	All in ER	1,182	NR	55.2	*Bacillus stearothermophilus*, *Streptococcus pyogenes*, *Escherichia coli*§
	Urine	NR†	Mainly adults	All out patients	203	NR	25.1	*B. stearothermophilus*, *S. pyogenes*, *E. coli*§
Nepal[17]	Urine	2001	Adults	Febrile patients	806	19	38	*B. subtilis*, *S. pyogenes*, *E. coli*
Laos[16]	Urine	2005	Children and adults	Specific febrile illness‖	2,058	NR	49.7	*B. stearothermophilus*, *S. pyogenes*, *E. coli*§
	Urine	2005	Children and adults	All out patients	1,153	24	36.2	*B. stearothermophilus*, *S. pyogenes*, *E. coli*§
Thailand[30]	Serum	2005–2008	Children and adults	Pneumonia and sepsis	NR¶	27.3	23.6#	*S. aureus*
Multiple countries[33] **	CSF	2006–2007	Children < 5 years	Meningitis	939	NR	33**	*Kocuria rhizophila*
Nigeria[22]	Serum	2008–2009	Children < 5 years	Bacteraemia	126	NR	55.6	*Micrococcus luteus*
Cambodia[15]	Urine	2011	Children (≤ 16 years/o)	All out patients	775	NR	31.7	*B. stearothermophilus*, *S. pyogenes*, *E. coli*§
Multiple countries[11] ††	Serum	2011–2014	Children < 5 years	Severe pneumonia	3,995	NR	25.6††	*S. aureus*
The Philippines (current study)	Urine	2015	Children and adults	ER attendees with fever	410	36.8	40.0	*B. stearothermophilus*, *S. pyogenes*, *E. coli*§

ALRI = acute lower respiratory infection; ER = emergency room; HIV = human immunodeficiency virus; NR = not recorded.
* Published 1990.
† Published 1999.
‡ 11% (fatal illness), 8.6% (severe illness), and 3.5% (non medical problems).
§ *B. stearothermophilus* (ATCC 7953), *S. pyogenes* (ATCC 19615), and *E. coli* (ATCC 25922).
‖ CNS infection, septicaemia typhus nonmalarial causes of fever.
¶ 35,639 blood culture were taken.
\# 14% children < 5 years.
** Pakistan 12% (Pakistan), 53% (Bangladesh), and 30–35% (African sites).
†† Bangladesh (23.9%), Gambia (7.4%), Kenya (13.0%), Mali (19.2%), South Africa (HIV infected: 58.2%, HIV uninfected: 48.8%), Thailand (19.2%), and Zambia (HIV infected: 36.4%, HIV uninfected: 28.8%); 763 (18.3%) enrolled subjects had antibiotic treatments in the study sites before the sample collections.

patients which were relied on clinical diagnosis by the attending physicians in the SLH.

CONCLUSION

This study, conducted in a densely populated, low-income, and dengue endemic area in Manila, provides further evidence that a significant proportion of patients presenting to hospital with fever have already taken antibiotics. Interestingly the lowest-income group was more likely to use antibiotics compared with other groups. Further studies are needed to clarify the impact of education on the proper management of acute febrile illness to reduce unnecessary antibiotic use in a low-income population.

Received July 15, 2017. Accepted for publication September 24, 2017.

Published online March 5, 2018.

Acknowledgments: We are grateful to all the patients who participated in the study, the doctors, and nursing staff of the emergency room of the San Lazaro Hospital. This study was part of the San Lazaro Hospital-Nagasaki University Collaborative Research Partnership funded by the Government of Japan.

Financial support: The study was funded by the Ministry of Education, Culture, Sports, Science and Technology, and the Government of Japan. The funders had no role in the study design, data collection and analysis, decision to publish, or reparation of the article.

Disclosure: Part of this work was submitted as a Master of Tropical Medicine thesis by Dr. Noriko Takamura, School of Tropical Medicine and Global Health, Nagasaki University, Japan. This work was presented in part at American Society of Tropical Medicine Meeting, November 2016.

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